

II. **REMARKS**

Claims 1-9 are pending in this application. Claims 2, 5, and 6 are withdrawn. By this Amendment, claims 1, 4, and 9 are amended. The amendments are supported by the specification and the claims as originally filed. Claim 4 is amended to correct typographical errors and the amendments to claims 1 and 9 are supported, for example, by the originally filed claims 1 and 9, the second full paragraph on page 1 of the specification, and the first full paragraph on page 30 of the specification. No new matter is added.

Entry of this Amendment is proper under 37 C.F.R. §1.116 since this Amendment: (a) places the application in condition for allowance for reasons discussed herein; (b) does not raise any new issue regarding further search and/or consideration since the Amendment amplifies issues previously discussed throughout prosecution; (c) does not present any additional claims without canceling a corresponding number of finally-rejected claims; and (d) places the application in better form for appeal, should an appeal be necessary. Entry of the Amendment is thus respectfully requested.

Claims 1, 3, 4, and 7-9 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. This rejection is traversed.

Applicants agree with the Examiner that the specification is "enabling for reducing the degenerative effects on cartilaginous matrix" (Final Office Action, page 3). Further, Applicants respectfully submit that this rejection is overcome by the above amendments to the claims, which were made in order to expedite prosecution.

Accordingly, for at least the above reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 3, 4, and 7-9 under 35 U.S.C. § 112, first paragraph, for lack of enablement.

Claims 1, 3, 4, and 7-8 are rejected under 35 U.S.C. § 102(b) as being anticipated by Armour et al. ("Inhibition of bone resorption in vitro and prevention of ovariectomy-induced bone loss in vivo by flurbiprofen nitroxybutylester (HCT 1026)," *Arthritis and Rheumatism*, 44(9):2185-2192 (Sept. 2001)). This rejection is respectfully traversed.

Applicants respectfully maintain that Armour et al. does not disclose the method of present claim 1. Dependent claims 3, 4, 7, and 8 are patentable for at least the same reasons as independent claim 1. Present claim 1 discloses "[a] method of reducing degeneration of the cartilaginous matrix comprising administering to a subject with arthritis an effective amount of one or more compounds or salts thereof having the following formula: A-(B)_{b0}-(C)_{c0}-N(O)_s (I)" (emphasis added). Applicants respectfully submit that the phrase "degeneration of the cartilaginous matrix" in present claim 1 does not include bone loss in a joint due to bone resorption or osteoclast formation.

Cartilaginous matrix relates to cartilage (see, e.g., the first full paragraph on page 30 of the specification, disclosing "reducing ... cartilage degeneration process in arthritic disease"), a type of connective tissue generally found in the joints and around bones. Applicants enclose three medical dictionary excerpts, which disclose that "cartilaginous" means "resembling cartilage," "cartilage matrix" is the "[t]he intercellular substance of cartilage consisting of fibres and ground substance," and that "ground substance" is

"amorphous material in which structural elements occur; in connective tissue, it is composed of proteoglycans, plasma constituents, metabolites, water, and ions present between cells and fibres." There is no reference to bones or joints in these definitions. In contrast, bone resorption is generally described as the process by which osteoclasts break down bone and release the minerals, resulting in a transfer of calcium from bone fluid to the blood.

Further, the compounds of formula (I) of the method of present claim 1 are capable of counteracting the progressive reduction of the chondrocytes responsiveness to TGF (transforming growth factor)- β by inducing expression of the TGF- β proteins. The degeneration of the cartilaginous matrix is thereby reduced in view of the known stimulating effects of TGF- β on matrix synthesis. See, e.g., the first and second full paragraph on page 3 of the specification and pages 256 and 260 of N. Felisaz et al., *Osteoarthritis and Cartilage* (1999) 7:255-267 (enclosed). As such, the effect on cartilage of the presently claimed invention and the effect due to intimate connection between bone and cartilage are different and independent.

As previously noted, Armour et al. merely discloses *in vivo* administration of HCT1026 (flurbiprofen nitroxybutylester) to a mouse model of ovariectomy-induced bone loss and that it inhibited interleukin-1-induced bone resorption and osteoclast formation (Armour et al., page 2185, Abstract). As such, Armour et al. merely discloses the effect of HCT1026 on osteoclast cells in bones. Applicants agree with the Examiner that "Armour et al. is silent to the effect on HCT1026 on chondrocytes found in cartilage" (final Office Action, page 10). As such, Applicants submit that Armour et al. is silent as

to reducing degeneration of the cartilaginous matrix as in the method of the presently claimed invention.

As Armour et al. does not disclose each and every element of the presently claimed invention, Applicants respectfully submit that Armour et al. does not anticipate the presently claimed invention. Accordingly, for at least the above reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 3, 4, and 7-8 under 35 U.S.C. § 102(b) as being anticipated by Armour et al.

III. **CONCLUSION**

Applicants respectfully submit that this application is in condition for allowance and such action is earnestly solicited. If the Examiner believes that anything further is desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned representative at the telephone number listed below to schedule a personal or telephone interview to discuss any remaining issues.

In the event this paper is not considered to be timely filed, Applicant hereby petitions for an appropriate extension of time. The fee for this extension may be charged to our Deposit Account No. 01-2300, referring to Attorney Docket No. 026220-00055. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 01-2300, referencing Attorney Docket No. 026220-00055.

Respectfully submitted,



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Enclosures: References (4)